

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: AWADHESH K. MISHRA CONFIRMATION No.: 7018
SERIAL No.: 09/321,766 EXAMINER: FAY, ZOHREH A
FILING DATE: May 28, 1999 ART UNIT: 1627
FOR: THERMOPROTECTED COMPOSITIONS AND PROCESS FOR
TERMINAL STEAM STERILIZATION OF MICROPARTICLE
PREPARATIONS

Via EFS-Web

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Applicants request review of the final rejection of the claims mailed March 20, 2012. A Notice of Appeal is being filed concurrently with this paper. Authorization for payment of the fee for a one-month extension of time accompanies this paper.

The claimed invention provides an aqueous microsuspension of a water insoluble (or poorly soluble) drug that is stabilized against the particle size growth (or flocculation or agglomeration) that occurs following steam sterilization of such compositions. This is achieved by the inclusion of a phospholipid and a water soluble polyhydroxy thermoprotecting agent (*e.g.*, trehalose, lactose, dextrose, sorbitol, dextran, mannitol and mixtures thereof) in the composition. The claimed compositions are further devoid of surfactants that require elevation of their cloud point temperature by addition of a cloud point modifier as well as other surfactant additives which coagulate upon steam sterilization.

The rejection under 35 USC § 103(a) of claims 21-24, 28-38, 40-42, 46, 48-54, 56, 57, 63-66, and 68-75 as unpatentable over US 5,858,410 (“Muller”) in view of US 5,739,152 (“Anderson”) should be withdrawn because the combination fails to establish a *prima facie* case of obviousness with respect to independent claims 21 and 22. And further, or in the alternative, the finality of the rejection should be withdrawn because the Examiner failed to fully consider Applicants’ remarks made in their last reply (the response filed January 20, 2012).

Muller illustrates both the problem of instability in the form of particle size growth following steam sterilization of particulate suspensions and the unpredictability of surfactant

effects on that instability. The problem is evidenced in both Examples 10 and 12 of Muller. In Example 10, Muller shows that compositions containing 0.3% Tween and mannitol were not stable. As noted by Muller, “[t]he number of particles greater than 5 μm rose as a result of exposure of the nanosuspensions to heat and the resulting formation of aggregates.” Muller at col. 15, lines 53-55. It was only by diluting the compositions with 2 parts or 9 parts water that stabilization was achieved. This is consistent with the results shown in Example 12 of Muller, but entirely unpredictable based upon theory. In Example 12, Muller compares the stability of formulations containing decreasing amounts of Tween (from 1% to 0.03%) and the same amount of mannitol. The highest amount of Tween (1%) “already showed macroscopic visible aggregates after autoclaving” and “[s]urprisingly, the nanosuspensions showed a higher stability with decreasing surfactant concentration.” Muller at col. 16, lines 63-67. This was unexpected because, based on theory, stabilization should have occurred with higher amounts of surfactant. *See* Muller at col. 7, lines 30-34. This observation in Muller underscores the unpredictability in the art with respect to the effects of an added surfactant (in this case Tween) on the stability of a system of a nanosuspension of a particulate active and a thermoprotecting agent (*e.g.*, mannitol) undergoing steam sterilization. Indeed, Figure 17 shows that even 0.3% Tween exhibited a significant growth in particle size after autoclaving, consistent with the results discussed in Example 10. The Examiner’s position that Muller describes the combination of a phospholipid with a polyhydroxy thermoprotecting agent (*e.g.*, trehalose) is based upon her misreading of the claims of Muller, which do not in fact encompass that embodiment. Instead, and consistent with the disclosure of Muller, the claims only encompass separate embodiments in which either a phospholipid (claim 14) or trehalose or mannitol (claim 22) are used in the composition. Neither the claims nor the description of Muller point to a composition containing both. Muller exemplifies phospholipid-containing nanosuspensions (the phospholipid is lecithin) in Examples 14-16. But notably, these compositions lack a polyhydroxy thermoprotecting agent and none are subjected to steam sterilization. The skilled person could not reasonably have predicted based on Muller that any of these compositions would actually be stable against particle size growth during steam sterilization. Indeed, each of these compositions contains 0.3% phospholipid, an amount of surfactant that was shown by Muller, in the case of Tween, to result in unacceptable particle size growth. Moreover, there is nothing to suggest further adding a polyhydroxy

thermoprotecting agent to these compositions, as required by the claims. In summary, and contrary to the Examiner's unsubstantiated assertion, Muller fails to describe or suggest the claimed combination of a phospholipid and a polyhydroxy thermoprotecting agent in a composition stabilized against particle size growth during steam sterilization; nor does Muller provide a reasonable expectation of success in making that combination.

Andersson does not cure the deficiencies of Muller because Andersson describes only phospholipid-containing pharmaceutical emulsions. *See e.g.*, Andersson at col. 6, lines 62-67 (emphasis added). The successful terminal steam sterilization of phospholipid-stabilized emulsions is noted by Applicants' specification and does not provide a reasonable expectation of success in modifying Muller to obtain a particulate suspension containing both a phospholipid and a polyhydroxy thermoprotecting agent. *See* the specification at p. 2, para. 2. The emulsions described by Andersson do not comprise particles of the active. Instead, the active is dissolved in the lipid phase. *See e.g.*, Andersson at col. 6, lines 15-16. Accordingly, such emulsions are not subject to the same physical instability following steam sterilization as the particulate suspensions of Muller and therefore success in formulating such emulsions to be stable after steam sterilization cannot be reliably and predictably translated to the problem of stabilization of particulate suspensions against particle size growth. Accordingly, the combination of Andersson with Muller does not remedy the skilled person's lack of a reason to modify the compositions of Muller as urged by the Examiner to combine a water soluble polyhydroxy thermoprotecting agent with a phospholipid or her lack of a reasonable expectation of success in doing so based on the unpredictability of surfactant effects on a system of a particulate suspension and polyhydroxy thermoprotecting agent as exemplified by Muller itself.

Claims 64 and 65

Dependent claims 64 and 65 are treated separately here because the combination of Muller and Andersson fails to describe or suggest an injectable aqueous terminally steam sterilized composition of a particulate suspension of a water insoluble or poorly soluble biologically active substance which consists of the biologically active substance, said one or more phospholipid surface modifiers, and said polyhydroxy thermoprotecting agent. None of the compositions described in the combination of references consists of the active, a phospholipid,

and a polyhydroxy thermoprotecting agent, as claimed. Accordingly, reconsideration and withdrawal of the rejection as applied to claims 64 and 65 is respectfully requested.

Examiner's Failure to Consider Applicants Arguments

In addition to the remarks above, Applicants wish to note the Examiner's failure to fully consider their remarks made in the response filed January 20, 2012. First, a number of the Examiner's statements ostensibly in reply to Applicants' remarks were made in reply to remarks not made in their January 20, 2012 response. This is evidenced by the Examiner's reference to arguments made by the Applicants regarding "newly added claims" specifying specific thermoprotecting agents such as trehalose and specific phospholipids such as egg, soy, or lipid E80. Final Office action at pages 4-5 (bridging para.). The claims referred to are claims 69 and 70 which were not newly added in the January 20, 2012 response. This is further evidenced by the Examiner's reference to remarks concerning the Lawrence article which were not made in the January 20, 2012 response. To the extent that the Examiner addressed any of the remarks actually made in Applicants' last reply she does so only with conclusory statements that do nothing to rebut Applicants' arguments. Thus, the Examiner merely re-states her "position" that Muller teaches the combination of a phospholipid with a polyhydroxy thermoprotecting agent (trehalose), without addressing Applicants' arguments to the contrary. To summarize, the Examiner's "position" is based upon her incorrect reading of the claims in Muller, which do not read on a composition in which trehalose is combined with lecithin, as urged by the Examiner. Similarly, the Examiner merely re-states her opinion that Muller "does not address any instability" associated with steam sterilization, contrary to the evidence of record showing that Muller clearly does address the instability of particle size growth, as discussed above and in Applicants' January 20, 2012 response. And finally, regarding the unpredictability exemplified by Example 12 of Muller, the Examiner again fails to address Applicants' point and instead simply states that the example "does not teach the lack of surfactants", which is inopposite. In summary, the finality of the March 30, 2012 Office action was improper at least because the Examiner failed to fully consider and respond to Applicants' remarks made in their January 20, 2012 response.

Applicant: Mishra
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In summary, it is submitted that the rejection under 35 USC § 103(a) of claims 21-24, 28-38, 40-42, 46, 48-54, 56, 57, 63-66, and 68-75 as unpatentable over US 5,858,410 (“Muller”) in view of US 5,739,152 (“Anderson”) should be withdrawn because the combination fails to establish a *prima facie* case of obviousness with respect to independent claims 21 and 22. In the alternative, it is requested that the Examiner withdraw the finality of the current Office action and fully address Applicants’ remarks made in their response filed January 20, 2012.

Respectfully submitted,

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